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EXAMINER	
CAPUTA, A	

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DATE MAILED: 09/07/94

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 6/10/94, 6/18/94, 8/8/94 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449. 7 pgs
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 1-18 are pending in the application.
   Of the above, claims 2, 3, 6, and 9-11 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1, 4, 5, 7, 8, and 12-18 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

Part III DETAILED ACTION

Election/Restriction

1. Applicant's election of Group I, Claims 1-9, 12-17, species g of PB2-SEQ ID Nos. 15 and 29 in Paper No. 13 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (M.P.E.P. § 818.03(a)).

2. Claims 10, and 11 are withdrawn from further consideration by the examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention. Claims 2, 3, 6, and 9 read on particular combinations of nucleic acids a non-elected species. Accordingly, said claims are withdrawn from consideration. Claims 1, 4, 5, 7, 8, 12-18 will be examined only to the extent that the claimed invention reads on the nucleic acid sequence comprising PB2 (SEQ ID Nos 15 and 29), the species elected by applicants.

Information Disclosure Statement

The information disclosure statement received fails to comply with the provisions of MPEP 609 because no copy of the abstract of Herlocher et al., abstract of Castrucci, article of Kilbourne, article by WHO was provided. The IDS has been placed in the application file, but the information referred to therein of said abstracts and said articles have not been considered as to the merits. Further it is requested by the Examiner that the month of said abstracts be provided to determine if the reference is before or after the filing date.

Specification

3. The use of trademarks such as B-D Vacutainer brand Winged Collection Set or SST (see page 37), Lysol (see page 36), KimWipe (see page 34), Oakridge tubes (see page 34), Speedvac concentrator (page 34) have been noted in this application. These and other trademarks should be capitalized (i.e. LYSOL) wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

4. The disclosure is objected to because of the following informalities: The accession numbers of the the wild type and cold adapted strain described on page 1 of the specification are not provided. Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. Claims 1, 4, 5, 7-8, 12-14, 17, and 18 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1, 4, 5, 7-8, 12-14, 17, and 18 are rejected since it is not clear if the nucleic acid comprises only those sequences recited or other sequences of genes which encode for other antigens of influenza not claimed and/or sequences of genes encoding foreign antigens. Further, said claims are rejected for being in an improper Markush format. The Examiner recommends the use of the phrase "...consisting of ..." with the use of the conjunction "and" rather than "or" in listing the species. See MPEP 706.03(Y).

b. Claims 4 and 7 are rejected for the use of the term "complementary". Does the isolated nucleic acid complementary to

the sequence as recited encompass those DNA molecules which are 75, 90, and 99% complementary?

c. Claims 8, 12-14, are 17 are vague and indefinite since it is unclear what the metes of bounds of the claimed surface protein. Do applicants intend to limit the surface protein to NA or HA? Further it is unclear as to what constitutes as operatively linked.

d. Claims 1, 4, 5, 7-8, and 18 are rejected since it is not clear what the metes and bounds of the claimed "isolated nucleic acid". Do applicants intend to claim the isolated viral genome since the nucleotide sequence of the isolated nucleic acid is open ended and not limited to Seq ID No. 15.

e. Claims 1, 4, 5, 7-8, 12-14, 17, and 18 are rejected for the use of the term "nucleic acid". Since the sequences recited in the instant claims are DNA sequence or have a DNA sequence the isolated product as claimed does not encompass RNA, a nucleic acid.

Claim Rejections - 35 USC § 112/1st paragraph

6. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach one of ordinary skill in the art how to make and/or use the claimed invention, i.e. failing to provide an enabling disclosure.

The elected species is drawn to a nucleic acid and reassortant virus containing said nucleic acid which has at least one surface antigen of the wild type and the PB2 of the cold adapted virus. However, the specification provides sufficient guidance to the elected species as broadly claimed. From the prior art it appears that both the HA and NA are required from the wild type to be effective (see Cox et al., 1988) and more than a PB2 is required since other genes appear to contribute to attenuation (see Snyder et al.).

The specification teach using the ferret as a model to establish the wt 2(3) virus was attenuated (see page 13). Snyder et al. teach the ferret is not sufficient to predict the outcome of attenuation of the vaccine since ferrets have a normal body temperature higher than humans (see page 491). Accordingly, in view of the teachings of Snyder et al. it is unpredictable if the attenuation of the wt(2), cold adapted virus, reassortant, or the gene encoding the PB2 (wild type or cold adapted) as described in the specification is sufficiently attenuated for use in humans.

The claimed invention encompass a reassortant which contains the surface antigens of influenza B with the PB2 gene of the cold adapted influenza A virus. However, in view that the prior art (i.e. See Massab et al. Vaccine 3:355-369 1985) disclose using reassortants containing genes from either influenza A or B and not both and the specification provides no evidence of a reassortant containing genes from influenza A and B it unpredictable if such a reassortant would be useful as a vaccine.

8. Claims 1, 4, 5, 7-8, 12-18 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

9. The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention.

The specification lacks complete deposit information for the deposit of isolated wild type and cold adapted A/AnnArbor/6/60 vral strains as broadly claimed. Because it is not clear that the 2(3) virus encompassed in the claimed invetion are known and publicly available or can be reproducibly isolated from nature without undue experimentation and because the best mode disclosed by the specification requires the use of said virues, a suitable deposit for patent purposes is required. Accordingly, filing of evidence of the reproducible production of the said viruses encompassed in claims 15 and 16, is required. Without a publicly available deposit of the above viruses, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of said virues is an unpredictable event. Note that the best mode is not satisfied by a written disclosure unless the exact embodiment is reasonably reproducible from that disclosure. If reproducibility of the viruses is not established, failure to deposit said virues would result in concealment of the best mode contemplated by applicant for carrying out the invention. In re Sherwood, 615.2d 809,204 USPQ 537 (CCPA 1980).

Applicant's referral to the deposit of sadi viruses on page 1 of the specification is an insufficient assurance that all required deposits have been made and all the conditions of 37 CFR §1.801-1.809 have been met.

If the deposit has been made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the

deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposit will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository is required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State. Amendment of the specification to recite the date of deposit and the complete name and full street address of the depository is required. As a possible means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

Applicant's attention is directed to In re Lundack, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR §1.801-1.809 for further information concerning deposit practice.

10. Claims 15 and 16 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or

> on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

12. Claim 16 is rejected under 35 U.S.C. § 102(e) as being anticipated by Younger et al. (US Patent No. 5,149,531).

Younger et al. disclose of a cold adapted viral strain of A/Ann Arbor/6/60 isolated (see Column 5, lines 8-10).

13. Claim 16 is rejected under 35 U.S.C. § 102(b) as being anticipated by Buonagurio et al. (J. Virol. 49(2):418-425 1984)

Buonagurio et al. disclose of a cold adapted isolated A/AA/6/60 viral strain (see page 418; column 2)).

14. Claims 15 and 16 are rejected under 35 U.S.C. § 102(b) as being anticipated by Cox et al. (Virology 167:554-567 1988).

Cox et al. disclose a purified wild type and cold adapted A/Ann Arbor/6/60 virus (see Page 555; Column 1).

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

> Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

16. Claims 1, 4, and 18 are rejected under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Buonagurio et al. (J. Virol. 49(2):418-425 1984).

The claimed invention is directed to a isolated nucleic acid of a cold adapted strain of A/Ann Arbor strain comprising a recited sequence of PB2. Buonagurio et al. disclose a purified RNA and double stranded cDNA of a cold adapted A/AA/6/60. Buonagurio et al. appears to disclose the same nucleic acid sequence as claimed or an obvious or analogous variant of claimed isolated nucleic acid as broadly claimed. Buonagurio et al. does not characterize the properties of the nucleic acid (i.e. nucleic acid sequence). However, the mere discovery of a nucleic acid sequence imparts neither novelty nor unobviouness to the nucleic acid. Since Buonagurio et al. nucleic acid molecule is double stranded and one strand is complementary to the other strand it would have been reasonable to conclude the double stranded DNA disclosed by Buonagurio et al. has a nucleic acid which is complementary to the recited sequence.

17. Claims 1, 4, 5, 7, 8, 12, 13, 14, 17, and 18 are rejected under 35 U.S.C. § 103 as being unpatentable over Cox et al. (Virology 167:554-567 1988) and further in view of Belshe et al. (J. Infectious Disease 149(5): 735-740 May 1984 or Belshe et al. (J. Infectious Disease 165: 727-732 April 1992).

Cox et al. teach the entire nucleotide sequence (i.e. DNA sequence) for the PB2 gene of the wt and ca A/Ann Arbor/6/60 virus (see Figure 6, page 561, and Table 1). Cox et al. teach reassortant viruses that received the HA and NA from the wild type virus and the other genes of the ca parent are sufficiently attenuated, immunogenic and protective in humans (see page 554 and 565). Accordingly, it would have been obvious to one of ordinary skill in the art for one of ordinary skill that a vaccine for administration for humans encompass PB2 of the cold adapted donor since said gene contributes to the attenuation of reassorted virus. It is noted the claimed invention is directed to a PB2 sequence of a wild type virus and (cold adapted virus derived thereof) which was passaged through the egg twice and the PB2 sequence of the wild type virus as disclosed in the prior art was passaged in egg several times. While it is true that there may be difference in the nucleic acid sequence of the nucleic acid sequence of the PB2 of the prior art and as claimed it is reasonable to expect the that there are an obvious or analogous variant of each other since they appear to have the same functional properties (i.e. both appear to be useful as for the development of a vaccine comprising a reassortant which uses the cold adapted mutant as the donor strain and the HA and NA (surface antigens) are from an epidemic variant virus (wild type)).

Cox et al. does not teach of a method of preventing influenza in patients using the reassortants nor of using reassortant containing a wild type HA and NA from such wild type influenza viruses as California/10/78 (H1N1) virus, A/Kawasaki/9/86 (H1N1) virus, A/Korea/1/82, and B Texas/1/84.

Belshe et al. (J. Infectious Disease 149(5): 735-740 May 1984) teach a method of preventing influenza comprising a reassortant containing six genes of the cold adapted influenza

A/AnnArbor/6/60 virus and the HA and NA of the wild type California/10/78 (H1N1) virus.

Belshe et al. (J. Infectious Disease 165: 727-732 April 1992). teach a method of preventing influenza comprising a reassortant containing six genes of the cold adapted influenza A/AnnArbor/6/60 virus or B/AnnArbor/1/66 and the HA and NA of the wild type A/Kawasaki/9/86 (H1N1) virus, A/Korea/1/82, B Texas/1/84. It would have been obvious to one of ordinary skill in the art to use the method of immunization as described by Belshe et al. for reassortant as taught by Cox et al. or Belshe et al. since Belshe et al. teaches a method of immunization which is effective for a reassortant containing the cold adapted influenza A/AnnArbor/6/60 parent virus. It would have been obvious to one of ordianry skill in the art to optimize the dosage of the vaccine for maximal efficacy.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Anthony C. Caputa, whose telephone number is (703)-308-3995. The examiner can be reached on Monday-Thursday from 8:30 AM-6:00 PM. The examiner can be reached on alternate Fridays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Ms. Christine Nucker, can be reached on (703)-308-4028

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703)-308-0196.

Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the official Gazette 1096 OG 30 (November 15, 1989). The CMI Fax Center number is (703)-305-3014 or (703)-308-4227 [Back-up].

Anthony C. Caputa, Ph.D.

September 2, 1994

CHRISTINE M. NUCKER
SUPERVISORY PATENT EXAMINER
GROUP 180